Beyond the DNA: Comprehensive map of the human epigenome completed

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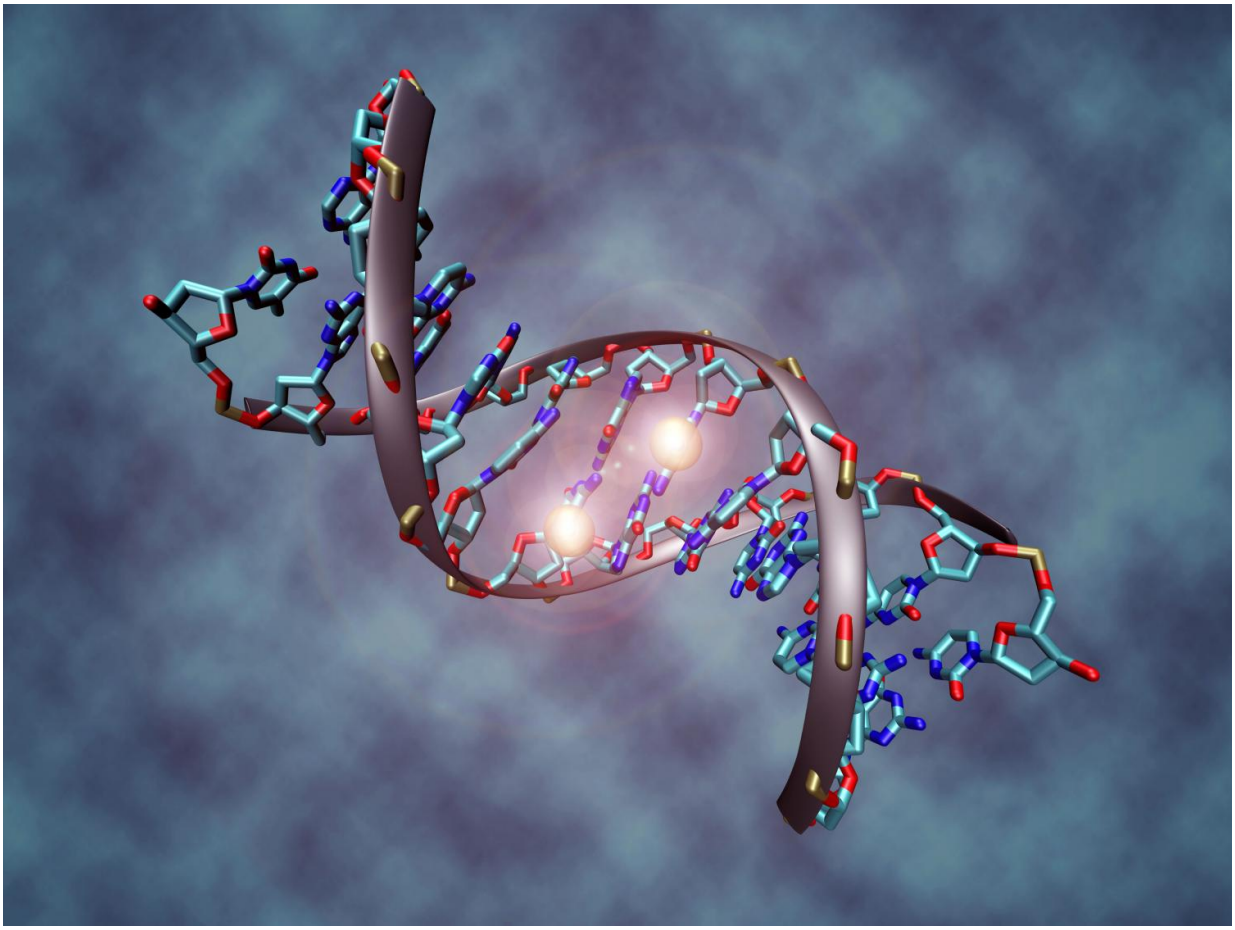


A methylated DNA molecule. DNA methylation plays an important role for epigenetic gene regulation in development and cancer. Credit: Christoph Bock/CeMM

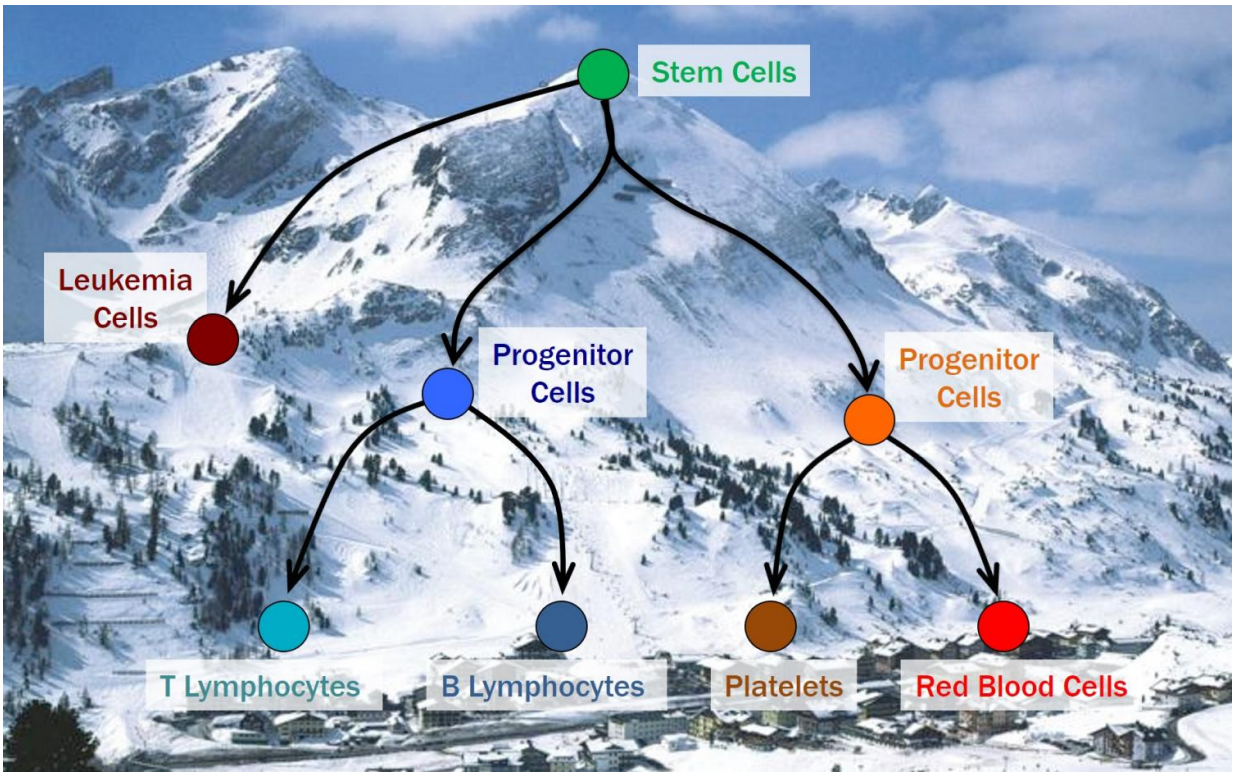
Scientists have established comprehensive maps of the human epigenome, shedding light on how the body regulates which genes are active in which cells. Over the last five years, a worldwide consortium of scientists has established epigenetic maps of 2,100 cell types. Within this coordinated effort, the CeMM Research Center for Molecular Medicine contributed detailed DNA methylation maps of the developing blood, opening up new perspectives for the understanding and treatment of leukemia and immune diseases.

One of the great mysteries in biology is how the many different cell types that make up our bodies are derived from a single cell and from one DNA sequence, or genome. We have learned a lot from studying the human genome, but have only partially unveiled the processes underlying cell determination. The identity of each cell type is largely defined by an instructive layer of molecular annotations on top of the genome - the epigenome - which acts as a blueprint unique to each cell type and developmental stage.

Unlike the genome the epigenome changes as cells develop and in response to changes in the environment. Defects in the factors that read, write, and erase the epigenetic blueprint are involved in many diseases. The comprehensive analysis of the epigenomes of healthy and abnormal cells will facilitate new ways to diagnose and treat various diseases, and ultimately lead to improved health outcomes.

A collection of 41 coordinated papers now published by scientists from across the International Human Epigenome Consortium (IHEC) sheds light on these processes, taking global research in the field of epigenomics a major step forward. These papers represent the most recent work of IHEC member projects from Canada, the European Union, Germany, Japan, Singapore, South Korea, and the United States. Three of these papers have been coordinated by Christoph Bock at CeMM.

The latest study from Christoph Bock's team, published today in the journal *Cell Stem Cell*, charts the epigenetic landscape of DNA methylation in human blood. Led by CeMM scientists Matthias Farlik and Florian Halbritter together with Fabian Müller from Max Plank Institute for Informatics, this study highlights the dynamic nature of the epigenome in the development of human blood.



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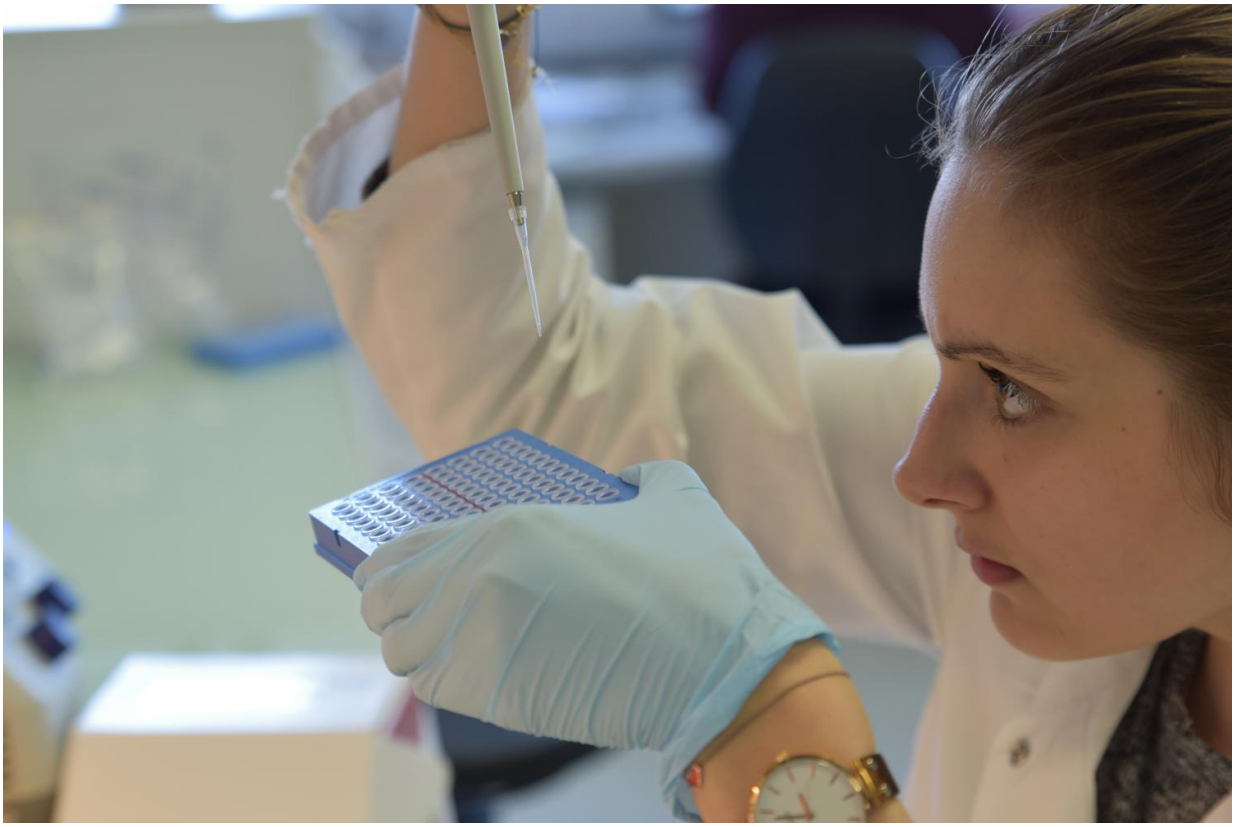
Our body produces billions of blood cells every day, which develop from a few thousand stem cells at the top of a complex hierarchy of blood cells. Using the latest sequencing and epigenome mapping technology, Bock's team now unraveled a blueprint of blood development that is encoded in the DNA methylation patterns of blood stem cells and their differentiating progeny.

This success was made possible by close international cooperation of European scientists: Blood donations of British volunteers were sorted by cell type by the team of Mattia Frontini at the University of Cambridge. These samples were shipped to Austria, where CeMM scientists performed the epigenome mapping. All data were then processed in Germany at the Max Plank Institute for Informatics and jointly analyzed by scientists at CeMM and at the Max Plank Institute for Informatics.

The result of the combined effort of Bock's team and many other members of IHEC is a detailed map of the human epigenome, similar to a three-dimensional mountain landscape: The stem cells reside on the mountain top, with valleys of cellular differentiation descending in many directions. As the cells differentiate, they pick one of several epigenetically defined routes and follow it downhill, eventually arriving at one specific valley, corresponding to a specialized cell type. Cells cannot easily escape these valleys, which provides robustness and protection against diseases such cancer.

Two other studies by Christoph Bock's team were published earlier this year and showcase how researchers are seeking to utilize epigenetic information for medicine. For instance, certain routes of differentiation are jammed in leukemia, such that cells can no longer reach their destination and take wrong turns instead. Surveillance of those cells by epigenetic tests can contribute to a more precise diagnosis of leukemia - clinical tests of this approach are ongoing.



A Scientist in the Laboratory of Christoph Bock investigates epigenome deregulation in leukemia. Credit: Wolfgang Däuble/CeMM

"The epigenetic map of the human blood helps us understand how leukemia develops and which cells drive the disease" says Christoph Bock. This is relevant to cancer diagnostics and personalized medicine, and it provides a compass for future efforts aiming to reprogram the epigenome of individual cells, for example by erasing critical epigenetic alterations from leukemia cells.

"The collection of manuscripts released by IHEC impressively demonstrates how epigenetic information and analyses can help find answers to pressing questions related to the cellular mechanisms

associated with complex human diseases", said Professor Hendrik (Henk) Stunnenberg from Radboud University, The Netherlands, former Chair of the IHEC International Scientific Steering Committee and coordinator of the EU-funded BLUEPRINT project.

More information: *Cell Stem Cell*, DOI: 10.1016/j.stem.2016.10.019